REMARKS

Applicants have canceled claims 34 and 40, amended claims 24, 36, 43, and 44, and added new claims 46-49. Support for claim 46 can be found, e.g., at page 2, line 4. Support for claim 47 can be found, e.g., at page 1, line 23. Support for claim 48 can be found, e.g., at page 2, line 1. Support for claim 49 can be found, e.g., at page 3, line 4. Support for the term "protein aeroallergen" as recited in claims 43 and 48 is inherent from the statement that the aeroallergen is encoded by a nucleic acid. Support for the limitation "orally" added to claims 24, 36, 43, and 44 can be found, e.g., in original claim 34.

Claims 24-33, 35-39, and 41-49 are pending. Applicants request reconsideration of these claims in view of the following remarks.

Obviousness Rejections in view of Hsu and Medalgini

The Examiner has rejected claims 24, 25, 28-34, and 43 as obvious in view of Hsu *et al.*. (U.S. Patent No. 5,958,891; "Hsu," herein) and Medalgini *et al.* (*Proc. Natl. Acad. Sci. USA* 1995; 92:6868-72; "Medalgini," herein). These rejected claims are directed to a method of suppressing IgE production.

As noted by the Examiner, Hsu *et al.* describes, for example, a method of decreasing IgE production by expressing a nucleic acid encoding the Derp5 allergen operably linked to a CMV promoter in mammalian cells. Medaglini describes a method of inducing IgA and IgG antibodies by expressing a hornet venom protein in *Streptococcus pyrogenes.* Regarding Medaglini, the Examiner notes in part:

> They administered the recombinant bacterial construct to mice orally and intranasally, and induced significant IgA and IgG immune response to the specific allergen. (emphasis added).

Applicant respectfully submits that the Examiner has not made a *prima facie* case of obviousness with respect to Hsu and Medaglini, for at least the following reasons.

The Examiner asserts that:

> [I]t would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by Medaglini *et al.* by simply substituting the plasmid pSMB7-M6 with the pCMV-Der p5 as taught by Hsu *et al.* with reasonable expectation of success. (emphasis added).

However, there was no expectation of success for the substitution suggested by the Examiner. First, the pCMV-Der p5 is a eukaryotic expression construct, designed for expression of Der p5 in mammalian cells, not for expression in a bacterial cell, such as the *Streptococcal gondii* cell as described in Medaglini.

Second, Medaglini's method does not disclose or suggest a system for suppressing IgE production. Rather, Medaglini's method "significantly" induces IgA and IgG immune responses. Thus, one skilled in the art, intending to suppress IgE production, would not have been motivated to use a system that induces IgA and IgG production.

Accordingly, Hsu and Medaglini do not render obvious the methods of claims 24, 25, 28-34, and 43.

Obviousness Rejections further in view of Casas and Kailasapthy

The Examiner has also rejected claims 24-45 in view of Hsu, Medaglini and Casas *et al.*. (US 6,100,388; "Casas," herein) and Kailasapthy *et al.*. (*Immunol and Cell Biol.* (2000) 78-80-88; "Kailasapthy," herein). As seen above, the combination of Hsu and Medaglini does not suggest a method of using Gram-positive bacterium to suppress production of IgE, as required by claims 24 to 43. Casas and Kailasapthy do not cure this deficiency of Hsu and Medaglini.

Casas teaches using lactobacilli as a vaccine, i.e., a vehicle to deliver an antigen. Casas's vaccine purportedly stimulates an animal to generate antibodies. Casas does not disclose nor suggest using lactobacilli to suppress IgE production.

Kailasapthy teaches feeding lactobacilli to milk-fed infants so that the lactobacilli "hydrolyse the complex casein" in milk to reduce exposure to allergens in infants (page 84, column 1, under "Food Allergy."). Thus, Kailasapthy also does not disclose nor suggest using lactobacilli to deliver an antigen to suppress IgE production.

For at least these reasons, the combination of Hsu, Medaglini and Casas and Kailasapthy do not render any of claims 24 to 43 obvious.

Applicants now address claims 44 and 45 which do not require suppressing the production of IgE molecules. Claims 44 and 45 include administering to a subject a lactic acid bacterium that expresses a dust mite allergen and expressing the dust mite allergen to relieve bronchopulmonary congestion upon exposure to the dust mite allergen. None of the four references discloses or suggests the use of a lactic acid bacterium to relieve bronchopulmonary congestion upon exposure to a dust mite allergen.

In conclusion, none of the cited references alone or in combination render the claimed methods obvious. Accordingly, Applicants respectfully request that all claims be allowed.

Enablement Rejection: Route of Administration

The Examiner has rejected claims 24-45 because the specification allegedly does "not reasonably provide enablement for . . . any aeroallergens, by any route of administration using any strain of gram-positive bacteria."

With respect to the route of administration, Applicants have amended the independent claims to include the term "orally."

Enablement Rejection: Aeroallergens

The Examiner has alleged that claim 43 embraces any aeroallergen, including industrial residues. Applicants have amended claim 43 to recite a "protein aeroallergen." Accordingly, claim 43 is drawn to a method that includes administering to a subject a non-pathogenic, Gram-positive bacterium that comprises (i) a nucleotide sequence that encodes a protein aeroallergen and (ii) a promoter operably linked to the nucleotide sequence. An allergen that is encoded by a nucleotide sequence is inherently proteinaceous.

Thus, as amended, the claim is not drawn any airborne particle but to protein aeroallergens that are encoded by nucleic acid (for example, a protein component of an airborne particle such as pollen).

A large number of protein aeroallergens were known in the art at the time that this application was filed. Non-limiting examples include:

- U.S. Patent No. 5,698,204 (IDS Item CD, issued December 16, 1997) and U.S. Patent No. 5,776,761 (IDS Item CF, issued July 7, 1998) which describe cDNAs encoding two

ragweed allergens: AmbaI, the major human allergen of ragweed, and AmbaII, and peptides derived from AmbaI and AmbaII.

- U.S. Patent No. 6,180,368 (IDS Item CK, issued January 30, 2001) and U.S. Patent No. 5,869,333 (IDS Item CG, issued February 9, 1999) which describe coding sequences for two ryegrass pollen antigens, Lol pIa and Lol pIb.
- Cosgrove *et al.* (IDS Item CQ, published June, 1997) describes a family of group I allergens from pollen. See, e.g., Figure 4 of Cosgrove.
- U.S. Patent No. 5,556,953 (IDS Item CC, issued September 17, 1996) which describes an allergen from the mold *Cladosporium herbarum*.
- U.S. Patent No. 6,048,962 (IDS Item CJ, issued April 11, 2000) which describes a nucleic acid sequence encoding an allergen from cats that is present in house dust.
- U.S. Patent No. 5,939,283 (IDS Item CH, issued August 17, 1999) which describes nucleic acid sequences encoding two allergens from dog dander.

The Examiner's attention is also directed to the numerous citations in the above documents. Accordingly, one skilled in the art, following the guidance of the specification, would be able to prepare a nucleic acid that encodes a protein aeroallergen operably linked to a promoter for expression as required by claim 43.

Enablement Rejection: Gram-Positive Bacteria

With respect to the strain of gram-positive bacteria, Applicants submit that the specification teaches numerous strains of gram-positive bacteria, including *Lactobacillus* (e.g., *L. acidophilus*, *L. casei*, *L. plantarum*, *L. fermentum*, *L. delbrueckii, L. johnsonii* LJI, *L. reuteri, Lactobacillus GG,* and *L. bulgaricus*), a *Streptococcus* (e.g., *S. thermophilus*), or a *Bifidobaterium* (e.g., *B. infantis, B. bifidum, B. longum, B. pseudolongum, B. breve, B. lactis* Bb-12, *and B. adolescentis*). See, for example, the paragraph beginning at page 1, line 19. Moreover, Applicants teach features of useful gram-positive bacteria, for example, (i) genera of human origin; (ii) stability against bile, acid, enzyme and oxygen; (iii) ability to adhere to intestinal mucosa; (iv) colonization potential in the human gastrointestinal tract; (v) production of antimicrobial substance; or (vi) demonstrable efficacy and safety. See, for example, lines 1-5,

page 3. One skilled in the art would be able to evaluate a gram-positive bacterium to determine if it satisfied at least one of these criteria.

The following are non-limiting examples of references that describe methods of evaluating Gram-positive bacteria and that were available prior to the filing date of this application:

- U.S. Patent No. 5,032,399 (IDS Item CA, issued July 16, 1991) describes a method of isolating bacteria from a human (e.g., column 2), a method for determining a bacterial strain's stability to acid and bile (e.g., column 2), a method of testing a bacterial strain's ability to adhere to gastrointestinal cells (e.g., column 3-4), a method of determining if a bacterial strain can exhibit "hardy growth" (e.g., column 4), and a method of using a gram-positive bacteria to colonize an intestine (see, e.g., column 7-8).
- U.S. Patent No. 5,494,664 (IDS Item CB, issued February 27, 1996) describes methods of evaluating implantation of bacteria in intestinal flora (e.g., column 3); methods of evaluating competitive exclusion of pathogenic bacteria (e.g., column 6); methods of testing in human volunteers, gnotoxenic mice, and gnotoxenic rats; and methods of evaluating adhesion to intestinal cells (e.g., column 3-5).
- U.S. Patent No. 5,709,857 (IDS Item CE, issued January 20, 1998) describes methods of characterizing the metabolic properties of bacterial strains (e.g., column 3-6), methods of evaluating growth a various pH (e.g., column 7), methods of evaluating resistance to bile (e.g., column 8), and methods of evaluating competitive exclusion of pathogenic bacteria (e.g., column 8-10).
- PCT WO 95/35389 (IDS Item CL, published December 28, 1995) describes methods for transforming lactic acid bacteria (see, e.g., page 14 et seq.).
- PCT WO 97/14802 (IDS Item CM, published April 24, 1997) describes methods for evaluating bacteria for an adhesive property and their application to evaluating "GRAS" (generally recognized as safe) bacterial strains (see, e.g., page 8).

In view of the teachings of the specification and the knowledge in the art at the time of filing, one skilled in the art would be able to select and use a gram-positive bacterium for the claimed methods. The Federal Circuit has recently asserted that a claim need not be limited to a particular type of bacteria where all of the methods needed to identify appropriate bacteria were

well known to those skilled in the art. *Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co.*, 228 F.3d 1338, 1345 (Fed. Cir. 2000) (also quoting *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed.Cir.1986) ("a patent need not teach, and preferably omits, what is well known in the art.")).

Where, as here, the level of skill in the art of selecting gram-positive bacteria is high, a skilled artisan would be able to follow the teaching of the specification and practice the invention as presently claimed.

Indefiniteness Rejections

The Examiner has rejected claims 24, 34, and 35 contending that the recitations in claims 34 and 35 are vague and indefinite because of the recitations "the allergen is administered orally" or "the allergen is administered as a yogurt." Applicants have canceled claim 34 and have amended claims 24 and 35. Applicants respectfully request that the rejections be withdrawn as moot.

Attached is a marked-up version of the changes being made by the current amendment. Enclosed is an Supplemental Information Disclosure Statement, a One-Month Petition for Extension of Time, a $194 check for excess claim fees, a $55 check for the Petition fee, and a $180 check for submission of the Supplemental Information Disclosure Statement. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 12774-002001.

Respectfully submitted,

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Version with Marked Changes

In the claims:

Cancel claims 34 and 40 without prejudice.

Amend claims 24, 35, 36, 43, and 44 as follows:

24. (Amended) A method of decreasing the production of IgE in a subject exposed to a dust mite allergen, the method comprising:

orally administering to a subject a non-pathogenic, Gram-positive bacterium that comprises (i) a nucleotide sequence that encodes a dust mite allergen and (ii) a promoter operably linked to the nucleotide sequence; and

expressing the allergen in the subject in an amount sufficient to suppress allergen-specific IgE production in the subject upon subsequent exposure to the allergen.

35. (Amended) The method of claim 34, wherein the [allergen] bacterium is administered [as] in a yogurt.

36. (Amended) A method of decreasing the production of IgE in a subject exposed to a dust mite allergen, the method comprising:

orally administering to a subject a lactic acid bacterium that expresses a dust mite allergen; and

expressing the allergen in the subject in an amount sufficient to suppress allergen-specific IgE production in the subject upon subsequent exposure to the allergen.

43. (Amended) A method of decreasing the production of IgE in a subject exposed to an protein aeroallergen [allergen], the method comprising:

orally administering to a subject a non-pathogenic, Gram-positive bacterium that comprises (i) a nucleotide sequence that encodes [an] a protein aeroallergen and (ii) a promoter operably linked to the nucleotide sequence; and

expressing the protein aeroallergen in the subject in an amount sufficient to suppress aeroallergen-specific IgE production in the subject upon subsequent exposure to the protein aeroallergen.

44. (Amended) A method of relieving bronchopulmonary congestion in a subject exposed to a dust mite allergen, the method comprising:

orally administering to a subject a lactic acid bacterium that expresses a dust mite allergen; and

expressing the allergen in the subject in an amount sufficient to relieve bronchopulmonary congestion in the subject upon subsequent exposure to the dust mite allergen.